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Botulinum toxin therapy for pain and inflammatory disorders: Mechanisms and therapeutic effects

Borodic GE; Acquadro M; Johnson EA

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Botulinum toxin (BTX) injections are a well-recognised therapeutic modality for the treatment of regional involuntary muscle disorders and recently BTX has been used for treatment of pain and inflammatory disorders. The primary purpose of this review is to discuss the mechanism of action of therapeutic BTX in light of both the traditional understanding of BTX pharmacological effects as well as new observations. The review will deal with clinical observations and relevant animal experimentation. The data and hypotheses presented are not only relevant to botulinum toxin technology but will certainly prove important in the basic mechanisms of some of the diseases where botulinum toxin has been successfully applied. BTX used clinically comprises botulinum neurotoxin (BoNT) complexed with non-toxic proteins. The non-toxic components of the BTX complexes stabilise the labile BoNT during purification and formulation as a therapeutic. The complex proteins may also have unrecognised clinical significance such as slowing diffusion in tissues or imparting stability. The mechanisms of BTX formulations acting on SNARE proteins are briefly reviewed providing a basis for BTX clinical applications. The potential for design of improved botulinum toxins and formulations is addressed.

KEYWORDS

BOTULINUM TOXIN A
PAIN
INFLAMMATION
EFFICACY
BLEPHAROSPASM
TORTICOLLIS
MEIGE SYNDROME
HEADACHE
HYPERSENSITIVITY
MOVEMENT DISORDERS
STABILITY
FORMULATIONS
PHARMACOLOGY
DYSTONIA
LETHAL DOSE
TRADEMARK

2001111578

Review of botulinum toxin type A and its clinical applications in migraine headache

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Expert Opin Pharmacother 2001;2(10):1649-1654

Botulinum toxin type A (BTX-A) has been used successfully for many disorders related to excessive muscle contraction. It works, in part, by causing a dose-dependent, reversible muscle relaxation. BTX-A has also been used for migraine prevention. The mechanism by which BTX-A acts in migraine is probably unrelated to its effect on muscle relaxation. BTX-A may have a distinct antinociceptive mechanism, either through action on the muscle spindles or through a direct effect on the central nervous system. Several trials and case reports have demonstrated the safety and efficacy of BTX-A in migraine headache. BTX-A is distinct from other preventive medications. Adverse events (AEs) are rare and mild. BTX-A is convenient, since the dosing interval may be 3 months or longer. However, before BTX-A can be considered a first-line agent for migraine, larger studies need to be conducted to determine optimum dosing and administration sites as well as patient characteristics that are predictive of response.

KEYWORDS

BOTULINUM TOXIN A
HEADACHE
EFFICACY
DRUG TOLERANCE
SAFETY
NEUROMUSCULAR JUNCTION
CHEMISTRY
ADMINISTRATION AND DOSAGE
MALE
FEMALE
TRADEMARK

2001081198

Treatment of palmar hyperhidrosis with botulinum toxin

Glogau RG

Semin Cutan Med Surg 2001 Jun;20(2):101-108

Excessive sweating of the palms, axillae, and soles can be managed with intradermal injections of botulinum toxin as an alternative to more aggressive surgical therapies such as sympathectomy and less effective techniques including topical antiperspirants. The dosage and injection techniques can be optimized to provide several months of freedom from this troubling disorder.

KEYWORDS

SWEAT
BOTULINUM TOXIN A
ADMINISTRATION AND DOSAGE
TRADEMARK

2000020183

Uses of botulinum toxin injection in medicine today. Regular review

Munchau A; Bhatia KP

Br Med J 2000 Jan 15;320(7228):161-165

Botulinum neurotoxin is produced by the anaerobic bacterium Clostridium botulinum. It is the most poisonous biological substance known. Very small amounts of botulinum toxin can lead to botulism, a descending paralysis with prominent bulbar symptoms and often affecting the autonomic nervous system. Botulism can occur in two ways. It can result from infection with bacterial spores that produce and release the toxin in the body-as in enteric infectious botulism, when the bacteria grow in the intestine, and in wound botulism, when the wound becomes infected. Alternatively, botulism occurs after ingestion of the toxin (food borne botulism). `Botulism has been recognized since the early 19th century, and there was speculation about what caused the condition. In 1822 it was suggested that a "fatty acid" in sausages was the culprit; and this led to the term botulism (botulus being the Latin word for sausage). In 1897, Van Ermengen related botulism to a bacterial toxin. `The discovery that botulinum toxin blocks neuromuscular transmission and thereby causes weakness laid the foundation for its development as a therapeutic tool. In 1981, the ophthalmologist Alan Scott pioneered treatment with botulinum toxin when he used it to treat strabismus. He paved the way for clinical research in many specialties. `Summary- points ` Botulinum toxin inhibits release of acetylcholine at the neuromuscular junction and in cholinergic sympathetic and parasympathetic neurones. `Local injections of toxin weaken overactive muscles and control hypersecretion of glands supplied by cholinergic neurones. `Botulinum toxin injections have an established role in some disorders of ocular motility. `Botulinum toxin is the treatment of choice for focal dystonias such as torticollis and writer's cramp and for hemifacial spasm and may complement the management of spasticity. `Local injections have also been shown to be beneficial in many other conditions including achalasia, chronic anal fissure, and hyperhidrosis. ` Treatment is usually well tolerated, the main side effect being weakness in adjacent muscles.

KEYWORDS

BOTULINUM TOXIN A
MOVEMENT DISORDERS
EYE MOVEMENTS
DYSTONIA
BOTULISM
PHARMACOLOGY
STRABISMUS
PAIN
COSMETIC TECHNIQUES
WRINKLES
SPHINCTERS
MUSCLE SPASTICITY
HEADACHE
OROMANDIBULAR DYSTONIA
LARYNGEAL DISEASES
DYSPHAGIA
STROKE
MULTIPLE SCLEROSIS

CEREBRAL PALSY
TREMOR
TIC
MUSCLES, SMOOTH

1: Cancer Chemother Pharmacol 1997;40(4):318-20 Related Articles, NEW Books, LinkOut

Pharmacokinetics of intrapericardial administration of 5-fluorouracil.

Lerner-Tung MB, Chang AY, Ong LS, Kreiser D.

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A 30-year-old patient with metastatic breast adenocarcinoma was diagnosed as having a malignant pericardial effusion. METHODS: The patient was treated with two courses of 200 mg 5-fluorouracil (5-FU) followed by 20 mg cisplatin 5 h later directly infused into the pericardial space through a catheter. The drug levels of the 5-FU were monitored during the second treatment. The half-life of 5-FU in the pericardial space was 168.6 min with a concentration of 0.113 mg/ml still detected at 5 h. The area under the curve (AUC) was estimated to be 4.739 mg h/ml. The plasma concentrations of 5-FU ranged from 0.022 to 0.04 mg/ml throughout the infusion. RESULTS: There was no significant change in the patient's blood counts or chemistry profile. She did not experience any side effects during the treatment. A pericardial window was performed 2 days later when balloon pericardiectomy was unsuccessful. The patient eventually succumbed to her disease 4 months later, but without evidence of pericardial effusion. CONCLUSIONS: We conclude that pericardial infusion of 5-FU allowed a high concentration of 5-FU to be achieved within the pericardial sac with a greatly increased half-life over that of systemic 5-FU treatment (168 min vs 6-20 min), and with little systemic toxicity.

PMID: 9225949 [PubMed - indexed for MEDLINE]

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1: Lung Cancer 1997 Mar;16(2-3):215-22

Intrapericardial cisplatin for the management of patients with large malignant pericardial effusion in the course of the lung cancer.

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National Institute of Tuberculosis and Lung Diseases, Warsaw, Poland.

Patients with cardiac tamponade or large malignant pericardial effusion, who survived longer than 30 days after withdrawal of catheter from the pericardial space, entered the study. Main goal of investigations was: evaluation of the effectiveness and side-effects of intrapericardial administration of cisplatin in cases with malignant pericardial effusion (MPE) and cardiac tamponade or large pericardial effusion in a course of the lung cancer. Sixteen patients (four women and 12 men), mean age 53 years, median age 57 years, range 27-70 years, entered this retrospective study. After pericardiocentesis and insertion of a polyurethane catheter, pericardial fluid was drained. Malignant etiology of pericardial fluid was confirmed by cytological examination and/or by echocardiography. The diagnosis of malignancy was based upon histological examination of samples obtained from primary tumor. After confirmation of MPE cisplatin (10 mg in 20 ml normal saline) was instilled over 5 min during 1-5 consecutive days (maximal total cisplatin dose in single course: 50 mg) directly into pericardial space. If a large pericardial fluid reoccurred the courses with intrapericardial administration of cisplatin were repeated. Treatment was considered successful if the patient with malignant effusion survived 30 days without recurrence of symptoms of large pericardial effusion and no other interventions directed to the pericardium were required. In 14 (87.5%) cases malignant pericardial effusion was confirmed by cytological analysis of pericardial fluid. In two cases echocardiography confirmed metastatic tumors to the pericardium. Positive effect of intrapericardial treatment with cisplatin was achieved in 15 cases (93.75%). Mean survival period in the whole group was 6.59 months (+/-6.2 months), median survival period was 3.7 months, range 2-24.1 months. There were no complications related to the pericardiocentesis. Transient atrial fibrillation was detected in three patients (18.8%). Mild nausea occurred in one case. No hypotension and retrosternal pain were observed. Cisplatin administered directly into pericardial space (CAP) seems to be effective and safe. No sclerosis of the pericardial space was observed after CAP.

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1: Clin Cardiol 1999 Jan;22(1 Suppl 1):I17-22

Intrapericardial treatment of inflammatory and neoplastic pericarditis guided by pericardioscopy and epicardial biopsy--results from a pilot study.

Maisch B, Pankuweit S, Brilla C, Funck RC, Simon BC, Grimm W, Herzum M, Hufnagel G.

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From a registry of 136 patients undergoing pericardiocentesis, 14 patients with autoimmune and 15 patients with neoplastic effusions were selected. All underwent pericardioscopy, epicardial and pericardial biopsy with histologic, immunohistologic, and polymerase chain reaction/or in situ hybridization analysis for microbial DNAs and RNA. Pericardioscopy identified neoplastic effusions by the high occurrence of protrusions. Fibrin threads and layers and neovascularization were found in both groups. For identification of the inflammatory and neoplastic process, the combined analysis of the cytology of the effusion and epicardial biopsy evaluation proved to be most important. Epicardial biopsy demonstrated a slightly higher sensitivity for identifying neoplastic disorders in the pericardium than cytology alone. Pericardial biopsy was inconclusive. Intrapericardial administration of 1 g of crystalloid triamcinolone in autoreactive pericarditis prevented recurrence in 13 of the 14 cases after 3 months and in 12 of the 14 cases after 1 year. In neoplastic effusion, intrapericardial administration of 50 mg cis-platin for 24 h prevented recurrence of a hemodynamically relevant effusion after 3 months in all, and after 6-12 months in 14 of 15 patients. Mortality in neoplastic effusion due to noncardiac tumor progression was 47 and 80%, respectively, after 3 and 6 months, as can be expected in endstage neoplastic disease. This pilot study demonstrates that local drug application is feasible, life-saving, and well tolerated by the patients. It opens perspectives for local drug application in other cardiac disorders as well.

PMID: 9929763 [PubMed - indexed for MEDLINE]

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